Official Title: A Multicenter, Randomized, Double-blind, Placebo-controlled clinical study to assess the efficacy and safety of Tildrakizumab in the treatment of moderate to severe plaque psoriasis of the scalp

Document: Statistical Analysis Plan (SAP)

NCT number: NCT03897088

Date: 30-Mar-2022

Statistical Analysis Plan

Study Part 1: Interim Analysis (up to Week 16)

Study Part 2: Double Blind (Week 16 to Week 52)

Study Part 3: Observational Safety Follow-Up (Week 52 to Week 72)

A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED CLINICAL STUDY TO ASSESS THE EFFICACY AND SAFETY OF TILDRAKIZUMAB IN THE TREATMENT OF MODERATE TO SEVERE PLAQUE PSORIASIS OF THE SCALP

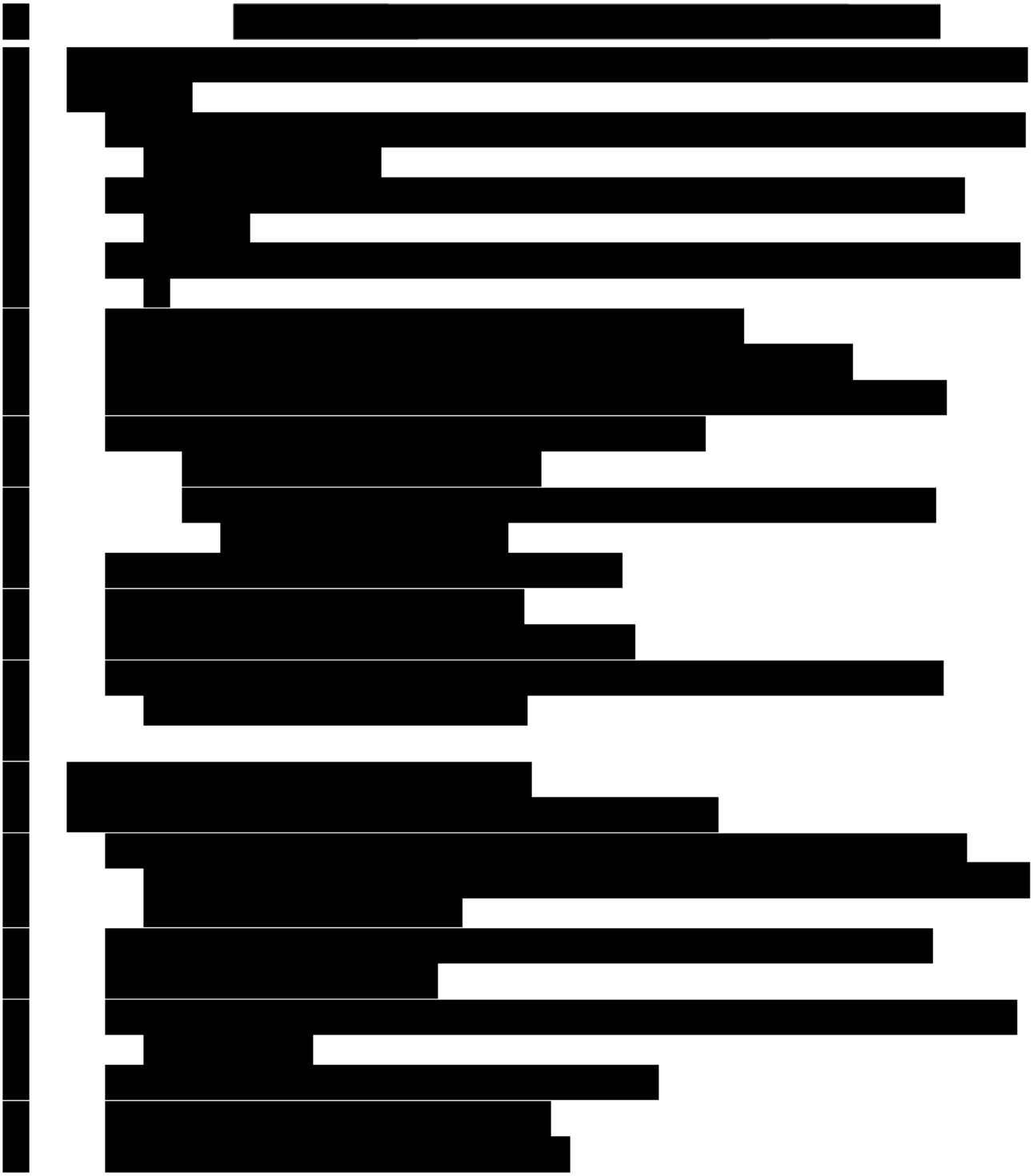
Protocol Number: TILD-18-20
[redacted]

IND Number: 101389

Date: 30-Mar-2022

[redacted]

[redacted]



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List of Abbreviations

Abbreviations	
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine transaminase
AST	Aspartate transaminase/serum glutamic oxaloacetic transaminase
BSA	Body surface area
CMH	Cochran-Mantel-Haenszel
C-SSRS	Columbia-Suicide Severity Rating Scale
CFR	Code of Federal Regulations
eCRF	Electronic case report form
CS	Clinically significant
DLQI	Dermatology Life Quality Index
ECG	Electrocardiogram
ECI	Event of clinical interest
EoS	End of study
EoT	End of treatment
ET	Early termination
FDA	Food & Drug Administration
ICH	International Conference on Harmonization
ICSR	Interim Clinical Study Report
IGA	Investigator Global Assessment
ITT	Intent-To-Treat
LOCF	last-observation-carried forward
M-N	Miettinen-Nurminen methodology
MACE	Major Adverse Cardiovascular Events
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
mIGA	Modified Investigator's Global Assessment
mITT	Modified Intent-To-Treat
MMRM	Mixed Model Repeated Measures
NCS	Not clinically significant
NRI	Non-responder imputation
NRS	Numeric Rating Scale
OC	Observed Cases
PASI	Psoriasis Area and Severity Index
PGA	Physician's Global Assessment
PGA-S	Physician Global Assessment of Skin
PN	Preferred Name
PP	Per Protocol
PSSI	Psoriasis Scalp Severity Index
PT	Preferred term
SAE	Serious adverse event

SAF	Safety analysis set
SD	Standard deviation
SOC	System organ class
TEAE	Treatment-emergent adverse event
uITT	Uniform Intent-To-Treat

1 INTRODUCTION

This Statistical Analysis Plan (SAP) Amendment has been developed following the review of Sun Pharmaceutical Industries Ltd Protocol TILD-18-20 (Version 01 Amendment 03, dated 17 Mar 2020), the corresponding case report form (CRF), SAP Version 2.0 (dated 09-June-2021).

This SAP describes the analysis sets and specific details for the statistical methods to be used for the analysis and reporting of all efficacy and safety data collected during the conduct of Protocol TILD-18-20 during the initial blinded treatment period to Week 16, double blinded active treatment period from Week 16 through Week 52, and observational safety follow-up from Week 52 to Week 72. This SAP reflects changes to the statistical considerations in the protocol. When needed, this SAP supersedes the statistical considerations identified in Protocol TILD-18-20 and its amendments (as applicable). Where considerations are substantially different, they will be identified as such in this document. [redacted]

This SAP is being written with consideration of the recommendations outlined in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E9 Guideline entitled “Guidance for Industry: Statistical Principles for Clinical Trials”, the E9 Addendum on Estimands and Sensitivity Analysis in Clinical Trials (R1) revision, and the most recent ICH E3 Guideline entitled, “Guidance for Industry: Structure and Content of Clinical Study Reports.”

2 STUDY OBJECTIVES

The objectives of this study are as follows:

2.1 Primary Objective

The primary efficacy objective of this study is:

- To assess the efficacy of tildrakizumab in subjects with moderate to severe scalp psoriasis, as measured by the proportion of subjects who achieve Investigator Global Assessment (IGA) mod 2011 (scalp) response from baseline at week 16. Response is defined as shown in Table 1 of Section 4.9.2 below.

The primary safety objective of this study is:

- To assess the safety and tolerability of tildrakizumab in subjects with moderate to severe plaque psoriasis of the scalp over 52 weeks.

2.2 Secondary Objectives

The key secondary objectives of this study are:

- To assess the efficacy of tildrakizumab in subjects with moderate to severe plaque psoriasis of the scalp, as measured by the proportion of subjects who achieve at least 90% improvement from Baseline in the Psoriasis Scalp Severity Index (PSSI) response at Week 16 compared with placebo.
- To assess the efficacy of tildrakizumab in subjects with moderate to severe scalp psoriasis, as measured by the proportion of subjects who achieve IGA mod 2011 (scalp) score of "clear" and "almost clear" with at least 2-point reduction from Baseline at Week 12 [redacted]
- To assess the efficacy of tildrakizumab in subjects with moderate to severe plaque psoriasis of the scalp, as measured by the proportion of subjects who achieve at least 90% improvement from Baseline in the PSSI response at Week 12 compared with placebo.
- [redacted]

- To assess the efficacy of tildrakizumab in subjects with moderate to severe scalp psoriasis, as measured by the proportion of subjects who achieve IGA (scalp only) of "clear" and "almost clear" with at least 2-point reduction from Baseline at Week 16.
- To assess the efficacy of tildrakizumab in the treatment of moderate to severe plaque psoriasis of the scalp compared with placebo as measured by scalp surface area (SSA) involvement at Week 16.
- To assess the effect of tildrakizumab on IGA mod 2011 (scalp) and PSSI at other measured time points through week 52.
- To assess the effect of tildrakizumab on IGA (scalp only), Scalp Itch NRS, PASI, PGA-S (whole body), and IGA mod 2011 (whole body), at week 12 and other measured time points through Week 52.
- To assess the time to response
- To assess the efficacy of tildrakizumab in the improvement of scalp itch as measured by the proportion of subjects achieving a 4-point reduction in Scalp Itch Numeric Rating Scale (NRS) score from Baseline at Week 16 compared with placebo
- To assess the efficacy of tildrakizumab in the treatment of moderate to severe psoriasis (entire body including scalp) compared with placebo as measured by Psoriasis Area and Severity Index (PASI), IGA mod 2011 (whole body), Physician Global Assessment for skin (PGA-S) score (whole body), and total body surface area (BSA) involvement at Week 16.

2.3 Exploratory Objective

The exploratory objective of this study is:

- To assess the effect of tildrakizumab on Quality of Life measured by: Dermatology Life Quality Index (DLQI).

3 OVERALL STUDY DESIGN AND TREATMENT PLAN

The overall study design and treatment plan are described in Sections 4.1 of Clinical Protocol TILD-18-20 [redacted]. A brief overview is included below.

This is a multicenter, randomized, double-blind, placebo-controlled Phase 3 study to assess the efficacy and safety of tildrakizumab in the treatment of moderate to severe psoriasis of the scalp. The study will enroll approximately 214 subjects with moderate to severe psoriasis

of the scalp. Eligible subjects will be randomized to 1 of the 2 arms [redacted] Arm A: Tildrakizumab 100 mg, subcutaneous (SC) (n=107) and Arm B: Placebo, SC (n=107).

The study will comprise 3 parts:

PART 1: Double-blind Placebo-controlled (Day 1 to Week 16)

After a Screening Period of up to 28 days and on Day 1, all eligible subjects will be randomized 1:1 to receive either tildrakizumab 100 mg or placebo administered by SC injection [redacted] Subjects should receive the first dose of study treatment within 24 hours of randomization. The treatment period for the double-blind placebo-controlled part of the study is 16 weeks. All assessments of efficacy and safety before or on the date of injection at Week 16 [redacted] are considered in PART 1.)

PART 2: Double-blind Active Treatment Extension (Week 16 to Week 52)

At Week 16, subjects initially randomized to placebo will be switched over to receive tildrakizumab 100 mg [redacted] while subjects initially randomized to tildrakizumab 100 mg will continue to receive tildrakizumab [redacted] In order to maintain the blind, subjects who were initially randomized to placebo will receive matching placebo injections [redacted] while subjects who were initially randomized to tildrakizumab will receive matching placebo injections at Weeks 20, 32, and 44. All assessments of efficacy and safety after the date of injection at Week 16 and before or on the date of injection at Week 52 [redacted] are considered in PART 2.

PART 3: Observational Safety Follow-up (Week 52 to Week 72)

After Week 52 [redacted] the study treatment should be stopped and all subjects, including those who terminated early from Part 1 and 2 will enter [redacted] Observational Safety Follow-up Period to monitor safety and tolerability [redacted] following last dose of study treatment. During the follow-up period, subjects should continue on study-approved concomitant medications only, however may be placed on appropriate therapies for safety concerns or significant worsening of psoriasis based on the judgment of the Investigator. The subjects will not receive study treatment during the follow-up period. [redacted]

4 STATISTICAL CONSIDERATIONS OF PROTOCOL

4.1 General Statistical Consideration

All summaries and analyses conducted will be by assigned therapy and/or combined total subjects. Data obtained on the eCRF and entered into the database will be provided in data listings showing individual subject values.

Descriptive statistics (number [n], mean, standard deviation [SD], median, first quartile [Q1], third quartile [Q3], minimum [min], and maximum [max]) for continuous variables and frequency distributions and percentages for discrete variables will be utilized. Categorical variables will be summarized by frequencies and percentages.

[redacted]

All tabulations of summary statistics, graphical presentations, and statistical analyses will be performed using SAS® Version 9.4 or higher.

4.1.1 Baseline and Study Day

For purpose of the SAP, Day 1 is defined as the date of first administration of study drug. Study day is calculated relative to the date of Day 1.

Unless otherwise specified, “Baseline” is defined as the last observed value of the parameter of interest prior to the first intake of study treatment (this includes unscheduled visits). For numerical variables, change from Baseline will be calculated as the difference between the post-Baseline value and the corresponding Baseline value. Change from Baseline is defined as: post-Baseline value – Baseline value. The percent change from Baseline will be calculated as change from Baseline divided by the Baseline value, expressed as a percentage.

4.2 Determination of Sample Size

The study will randomize approximately 107 subjects per treatment arm (Total N=214) [redacted] randomization to either tildrakizumab 100 mg arm (Arm A) or placebo arm (Arm B), [redacted]

[redacted]

340

[redacted]

4.3 Disposition of Subjects

The number and frequency of subjects who were screened, screen failures (overall and by reason of screen failure), randomized, completed (overall and by each part of the study), and discontinued (overall and by each part of the study) will be presented. A summary of reasons for discontinuation will be provided. [redacted] Due to the outbreak of COVID-19 pandemic, COVID-19 related subject disposition events will be further summarized per FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency (thereinafter referred to as FDA COVID-19 Guidance)[a], for the following:

- Number of subjects discontinued from the study for reasons related to COVID-19
- Number of subjects with visits altered (e.g., remote visits) or missed due to COVID-19
- Number of subjects with any efficacy assessments not done at each visit due to COVID-19 associated criteria.

[redacted].

4.4 Data Sets Analyzed

The following analysis sets will be used in the study:

Intent-to-Treat (ITT) Set: All randomized subjects who have been dispensed study [redacted]

Modified Intent-to-Treat (mITT) Set: [redacted].

[redacted]

Uniform Intent-to-Treat (uITT) Set: [redacted].

[redacted]

Safety Analysis Set (SAF): All randomized subjects who have received [redacted] dose of study treatment.

Per Protocol Set (PP): All subjects [redacted] who have completed the [redacted] placebo-controlled treatment without any major protocol deviation that could impact data interpretability for the primary efficacy endpoint. [redacted]

Safety endpoints will be analyzed descriptively based on the SAF, and subjects will be summarized based on the actual treatment they received.

4.5 Protocol Deviations

All protocol deviations (PD) will be tracked throughout the study and classified by deviation type, either minor or major. Protocol deviations represent a failure to adhere to the clinical study protocol. The two types of deviations are defined as:

- Minor protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that has not been approved by the IRB and which does not have a major impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.

- Major protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that has not been approved by the IRB and which has a major impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data. [redacted]

[redacted]

Prior to interim database freeze and final database lock, each deviation will be reviewed to determine if it excludes the patient from any of the analysis sets or any particular planned analysis. These determinations will then be described in the relevant clinical study report.
[redacted]
Minor protocol deviations will be presented as well. All deviations will be retained within the deviations tracker (considered the source document).

Protocol deviations attributable to the COVID-19 pandemic regardless whether deemed major or minor will be provided in a separate listing if deemed necessary. Protocol deviations will be presented in summary tables, for IA and overall, respectively.

4.6 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics generally will be summarized descriptively overall and by treatment in the ITT, mITT, uITT, SAF, and PP analysis sets. The following demographic and Baseline variables will be included:

- Age (years)
- Gender
- Race

- Ethnicity
- Prior use of TNF-alpha inhibitors (Yes/No)
- Weight (kg)
- Weight category (≤90 kg or >90 kg)
- Height (cm)
- BMI (kg/m^2)
- Baseline IGA mod 2011 (scalp) [redacted]
- Baseline IGA (scalp only)
- Baseline PSSI
- Baseline SSA involvement
- Baseline total BSA involvement
- Baseline IGA mod 2011 (whole body) [redacted]
- Baseline PGA-S score (whole body)
- Baseline Scalp itch NRS score
- Baseline PASI score

All demographic data and baseline disease characteristics data will be listed by subject.

4.6.1 Medical History

Medical/surgical history and concurrent procedures will be coded using the MedDRA (Medical Dictionary for Regulatory Activities) Version 24.0 or a more recent version and will be presented in a by-subject listing.

4.7 Prior/Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary September 1, 2019 B3 Global. Prior medications include medications used to treat the disease conditions and any other medications taken within 6 months prior to enrollment and stopped prior to start of treatment. Concomitant medications during the study are defined as any medications that are ongoing or with stop dates on or after date of first study medication administration.

For the determination of prior vs. concomitant medications, the following rules regarding the stop date will be applied:

- If the stop date is missing completely, the medication is assumed to be a concomitant medication.

- If only year was recorded, and it is before Baseline, it is a prior medication; if year is same or after Baseline, it is assumed to be a concomitant medication.
- If day is missing, but month and year are before Baseline, it is a prior medication; if month and year are the same as Baseline, it is assumed to be a concomitant medication; if month and year are after Baseline, it is a concomitant medication.
- If start date is after Baseline, it is a concomitant medication regardless.

[redacted]

The number and percentage of subjects taking prior medications or concomitant medications (overall and by study parts) will be summarized by anatomical therapeutic chemical (ATC) level 3 and preferred name (PN) for the SAF. Although a subject may have taken two or more medications, the subject is counted only once within an ATC classification. The same subject may contribute to two or more PTs in the same classification. All prior and concomitant medications will be listed by subject.

4.8 Study Drug Exposure and Compliance

Study drug exposure will be evaluated using total number of doses administered for the entire treatment period, and for Part 1 [redacted] at interim analysis and later, Part 2 [redacted] separately for final analysis. Number and percent of doses administered per subject and number of subjects with dose administered at each scheduled visit will be summarized with descriptive statistics by treatment arm (Part 1 only) and in total using the Safety Analysis Set.

[redacted]

The study medication was originally designed to be administered at the study center by trained staff; however, due to the outbreak of the COVID-19 pandemic, eligible and trained subjects could self-administer study medication during modified remote study visits. Self-administered study doses will be indicated in a listing.

All study drug administration data will be listed by subject.

4.9 Efficacy Analysis

4.9.1 Primary Estimand and Intercurrent Events

The primary estimand for this study is based on composite strategy approach. [redacted]

4.9.2 Analysis of Efficacy Variables

Efficacy endpoints will be summarized descriptively by randomized treatment and by visit for subjects within ITT, mITT, and uITT Sets as per the specifications below. The mITT will be considered as the primary population for primary efficacy analysis and the uITT and PP Sets as supportive; the ITT will be considered as the primary population for key secondary and all other efficacy endpoint analysis. The mITT and uITT Sets will be considered as the sensitivity analysis populations for primary efficacy analyses. Subgroup analyses incorporating multiple definitions of response may also be performed if sufficient subjects are identified to contribute to such analyses. [redacted].

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Details of imputation methods mentioned above and additionally are described in Section 4.9.3.2: Handling of Dropouts or Missing Data.

4.9.2.1 Primary Efficacy Analysis

4.9.2.1.1 Primary Efficacy Endpoint

[redacted]

[redacted] Treatment response is defined as an IGA mod 2011 (scalp) score of "clear" and "almost clear" with at least a 2-point reduction from Baseline at Week 16 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.9.2.1.1.1 Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint of IGA mod 2011 (scalp) response at Week 16 will be analyzed using the mITT Set and NRI imputation method. [redacted] he p-value from the CMH test comparing tildrakizumab 100 mg with placebo will be reported for inference.

[redacted]

Sensitivity analyses of the primary efficacy endpoint are described in Section 4.11 below.

4.9.2.2 Secondary Efficacy Analysis

4.9.2.2.1 Secondary Efficacy Endpoints

The key secondary endpoints are:

- The proportion of subjects achieving PSSI 90 [redacted] at Week 16
- The proportion of subjects achieving PSSI 90 at Week 12
- The proportion of IGA mod 2011 (scalp) score of "clear" or "almost clear" with at a least a 2-point reduction from Baseline at Week 12 [redacted]

[redacted]

These key secondary endpoints will be included in multiplicity adjustments.

Other secondary endpoints are:

- Mean percentage change in PSSI score from Baseline to Week 16
- The proportion of subjects achieving PSSI 75 [redacted] at Week 16
- The proportion of subjects achieving PSSI 100 [redacted] at Week 16.
- [redacted] to 100%.
- [redacted]
- Mean percentage change in scalp surface area involvement from Baseline to Week 16.
- Time to achieving IGA mod 2011 (scalp) response during the 16-week placebo-controlled treatment period, defined as time in days from Baseline to first achieving a score of "clear" or "almost clear" with at least a 2-point reduction from Baseline through Week 16. Subjects who have not achieved IGA mod 2011 (scalp) response by the last visit or Week 16 will be censored at their last available assessment or Week 16 assessment, whichever is later.
- Time to achieving PSSI 75 during the 16-week placebo-controlled treatment period, defined as time in days from Baseline to first achieving PSSI 75. Subjects who have not achieved PSSI 75 by the last visit or Week 16 will be censored at their last available assessment or Week 16, whichever is later.
- The proportion of subjects [redacted] decrease in Scalp itch NRS score from Baseline at Week 16, assessed among subjects with Baseline Scalp Itch NRS [redacted]

  The Scalp itch NRS is a self-administered, single item questionnaire with response options from 0=No Itch to 10=Worst itch imaginable.
- The proportion of subjects achieving PASI 75, PASI 90, and PASI 100 [redacted] at Week 16. Detailed PASI scoring algorithms are provided in Appendix 1 PASI Scoring.

[redacted]

- Mean percentage change in total BSA involvement from Baseline to Week 16.
- Change from Baseline at measured time points [redacted] Week 52 [redacted] for the following endpoints:
  - IGA mod 2011 (scalp)
  - PSSI
  - IGA (scalp only)
  - Scalp Itch NRS
  - PASI
  - PGA-S (whole body)
  - IGA mod 2011 (whole body)

[redacted]

4.9.2.2.2 Analyses of Secondary Efficacy Endpoints

Binary endpoints

The following binary endpoints will be analyzed in a similar manner as the primary efficacy endpoint based on the ITT [redacted] population as appropriate using NRI. A CMH test [redacted] will be used, [redacted]

- PSSI 90 at Week 16 (key secondary endpoint)
- PSSI 90 at Week 12 (key secondary endpoint)
- IGA mod 2011 (scalp) response at Week 12 (key secondary endpoint)
- IGA (scalp only) response at Week 16
- PSSI 75 at Week 16
- PSSI 100 at Week 16
- ≥4-point decrease in Scalp Itch NRS score from Baseline at Week 16
- PASI 75 at Week 16

- PASI 90 at Week 16
- PASI 100 at Week 16
- PGA-S response at Week 16

Continuous endpoints

The following continuous endpoints will be analyzed based on the ITT population using a mixed model for repeated measures (MMRM) procedure [redacted]

- Mean percentage change in PSSI score from Baseline to Week 16
- Mean percentage change in SSA involvement from Baseline to Week 16
- Mean percentage change in total BSA involvement from Baseline to Week 16

Treatment difference between tildrakizumab arm and placebo arm will be reported, [redacted]

Time to treatment response:

Time to IGA mod 2011 (scalp) response and time to PSSI-75 will be analyzed using the Kaplan-Meier method [redacted]

Other endpoints:

Change from Baseline for the following endpoints at measured time points [redacted] will be summarized in the mITT, [redacted] or ITT population as appropriate, using descriptive statistics:

- IGA mod 2011 (scalp)
- PSSI
- IGA (scalp only)
- Scalp Itch NRS

- PASI
- PGA-S (whole body)
- IGA mod 2011 (whole body)
- SSA involvement
- BSA involvement

[redacted]

4.9.2.3 Exploratory Efficacy Analysis

Exploratory efficacy endpoints include change from Baseline at measured time points through Week 52 [redacted] for DLQI score (total and 6 domain scores).

[redacted].

Exploratory efficacy endpoints also include subjects achieving IGA mod 2011 (scalp) response and PSSI 90 response [redacted]

The exploratory efficacy endpoint of the proportion of IGA mod 2011 (scalp) and PSSI 90 maintained response includes subjects with a response at Week 16 and maintained the response through Week 52.

All efficacy endpoints will be summarized for the ITT or mITT population using descriptive statistics for all scheduled visits, for each randomized treatment arm and overall.

4.9.3 Statistical / Analytical Issues

[redacted]

4.9.3.2 Handling of Dropouts or Missing Data

Data from subjects who withdraw from the study, including AEs and any follow-up, will be included in the analyses as applicable.

[redacted]

[redacted]

763 **4.9.3.3 Interim Analyses (IA), Data Monitoring and Primary Results Reporting**

764 Following the last subject's Week 16 visit, the IA (primary analysis) will be conducted on
765 available data to evaluate efficacy and safety.

[redacted]

[redacted]

4.9.3.4 Multicenter Studies

Descriptive summaries of the primary and key secondary efficacy endpoints will be presented for each individual study center to evaluate potential heterogeneity across sites.

[redacted]

[redacted]

4.9.4 Tabulation of Individual Response Data

All efficacy variables will be listed by subject.

4.9.5 Drug Dose, Drug concentration, and Relationships to Response

Not applicable.

4.9.6 By-Subject Displays

No individual subject profile data will be produced.

[redacted]

4.10 Safety Analysis

The safety and tolerability of the study drugs will be evaluated by reported adverse events (AEs), physical examinations, electrocardiogram results (ECGs), vital signs, laboratory test results (Hematology, Biochemistry, and Urinalysis), and Columbia-Suicide Severity Rating Scale (C-SSRS).

All safety summaries will be based on the Safety Analysis Set.

Following reporting of interim Week 16 results, a group comprising formerly placebo-treated subjects who migrate to tildrakizumab 100 mg for the remainder of the study will be identified for reporting at the end of the study.

4.10.1 Adverse Events

The incidence of treatment-emergent AEs (TEAE) will be summarized and tabulated by treatment group, MedDRA (Version 24.0 or higher) System Organ Class (SOC) and Preferred Term (PT). A TEAE is defined as an AE that first occurred or worsened in severity after the first administration of study treatment.

Several occurrences of the same AE in one subject will be counted once at the worst severity grade. [redacted]

The relationship of each AE to the study drug will be grouped as related (definitely, probably, possibly related) or unrelated (unlikely to be related, unrelated). Several occurrences of the same AE in one subject will be counted once and the one with the closest relationship to study medication will be counted. If an AE is missing the relationship to study medication, the event will be assumed to be related to study drug for analysis and summarization.

[redacted]

Non-TEAEs will be listed only and will not be included for analysis and summarization.

All AEs will be presented in a by-treatment and by-subject listing, detailing the verbatim term, SOC, PT, application site reaction or not, related to study indication or not, start date, stop date, time since most recent dose of IP, severity, outcome, relationship to study drug, action taken regarding study drug, action taken to treat AE, seriousness and criteria for seriousness. Serious AEs (SAEs) and TEAEs leading to study medication discontinuation, AEs of Special Interest (AESI), and events of clinical interest (ECI) will also be presented in separate listings.

An AE profile for the Safety Analysis Set will be provided for Part 1, Parts 2 and 3, and overall, which summarizes the subject incidence, by treatment received for the following information:

- Any TEAEs;
- Non-TEAEs;
- Drug-related TEAEs;
- Any TEAEs with an outcome of death;
- Treatment-emergent SAEs;
- Drug-related treatment-emergent SAEs;
- TEAEs leading to discontinuation of study medication;
- Drug-related TEAEs leading to discontinuation of study medication;

- Any AEs of special interest, including:
  - Injection site reactions
  - Severe infections
  - Malignancies (excluding carcinoma in situ of the cervix).
  - Non-melanoma skin cancer
  - Melanoma skin cancer
  - Major Adverse Cardiovascular Events (MACE)
  - Study treatment-related hypersensitivity reactions.

[redacted]

The number and percentage of subjects with TEAEs will be summarized for each treatment arm and/or in total by SOC and PT. Drug-related TEAEs, TEAEs leading to discontinuation of study drug, drug-related TEAEs leading to discontinuation of study drug, treatment-emergent SAEs, and drug-related treatment-emergent SAEs will be summarized in the same manner. For these summaries, subjects with multiple AEs will be counted only once per SOC and PT.

TEAEs by maximum severity and TEAEs by relationship to study treatment, and commonly occurring TEAEs, i.e., those that occur in [redacted] of the subjects in either treatment arm, will be summarized by SOC and PT by treatment received in Part 1, Parts 2 and 3, and overall.

Injection site reactions will be described in a by-subject listing and may be summarized separately if deemed necessary.

COVID-19 related adverse events may also be summarized separately if deemed necessary.

4.10.2 Clinical Laboratory Evaluation

Absolute values and changes from Baseline of clinical laboratory data (hematology, chemistry, continuous urinalysis parameter and lipids) will be summarized with descriptive statistics at Baseline, and Week 16 [redacted] at the interim [redacted]

All clinical laboratory data relevant to the reporting period [redacted] will be listed by subject. Values outside the normal ranges will be flagged. Flags will describe direction relative to normal range in relevant parameters.

4.10.3 Vital Signs

Vital signs measurements including temperature, pulse rate, systolic blood pressure, and diastolic blood pressure, respiratory rate at each scheduled visit and changes from baseline during the treatment period will be summarized by treatment arm. Vital signs will also be presented in a shift table displaying the cross tabulation of the Baseline result category versus the result of the post-treatment period at each scheduled visit. The categories of each vital sign parameters are as below:

[redacted]

4.10.4 12-Lead Electrocardiogram (ECG)

The ECG measurements at each scheduled visit [redacted] and change from baseline during the treatment period will be summarized by treatment arm.

All ECG measurements and the overall interpretation will be listed by subject [redacted]

4.10.5 Physical Examinations

The frequency of subjects with abnormal evaluations of body system findings for physical examinations will be summarized by visit and treatment group; abnormal physical examination findings will also be presented in a by-subject listing.

4.10.6 Performance Status

Not applicable.

4.10.7 Other Safety Parameters

The subjects will be assessed for suicidal ideation and behavior using Columbia-Suicide Severity Rating Scale (C-SSRS) at screening, baseline and each subsequent visit. C-SSRS contains two categories: (1) Suicidal Ideation (questions 1-5), most severe ideation will also be collected; (2) Suicidal behavior (questions 6-10).

The following outcomes are C-SSRS categories and have binary responses (yes/no). The categories listed below have been re-ordered from the actual scale in an increasing order of severity from 1 to 10 to facilitate the definitions of the comparative endpoints.

Table 2 C-SSRS Outcomes

Categories
Suicidal Ideation (1-5)
1 – Wish to be dead
2 – Non-specific active suicidal thoughts
3 – Active suicidal ideation with any methods (not plan) without intent to act
4 – Active suicidal ideation with some intent to act, without specific plan
5 – Active suicidal ideation with specific plan and intent

Categories
Suicidal behavior (6-10)
6 – Preparatory acts or behavior
7 – Aborted attempt
8 – Interrupted attempt
Suicidal acts (9-10)
9 – Non-fatal suicide attempt
10 – Completed suicide

The following are numerical scores derived from the above C-SSRS categories.

- Suicidal Ideation Score: The maximum suicidal ideation category (1-5 on the C-SSRS) present at the assessment. Assign a score of 0 if no ideation is present.
- Suicidal Behavior Score: The maximum suicidal behavior category (6-10 on the C-SSRS) present at the assessment. Assign a score of 0 if no behavior is present.
- Suicidal Ideation or Behavior Score: The maximum suicidal ideation or behavior category (1-10 on the C-SSRS) present at the assessment. Assign a score of 0 if no ideation or behavior is present.

Subjects are also classified into two risk levels:

- Intermediate risk level is indicated by a response of "yes" to Questions 1 to 3 and the absence of a "yes" response to Questions 4 and 5.
- High risk level is indicated by a response of "yes" to Questions 4 or 5 in the suicidal ideation section, or any positive response in the behavioral section of the C-SSRS.

Change in binary response to the questions from no to yes in any questions will be summarized in a shift table describing baseline vs post-baseline per visit, and worst post-baseline overall. Categorical scores will be analyzed similarly. C-SSRS risk levels are also summarized by visit. Results from the C-SSRS will be listed by subject. Results to Week 16 will be described in the Part 1 interim analysis, and overall results to Week 52 and 72 will be described in the final analysis.

4.11 Sensitivity and Subgroup Analyses

Sensitivity and subgroup analyses will be performed to confirm the robustness of primary analysis results.

[redacted]

[redacted].

[redacted]

common risk difference and the associated [redacted]

[redacted]

Tipping point analysis

A tipping point analysis under a missing not at random (MNAR) assumption will be performed as a sensitivity analysis to assess assumptions about any missing outcomes on the two treatment arms. [redacted]

[redacted]

4.12 COVID-19 Pandemic Impacted Subjects Assessment

COVID-19 impacted subjects will be identified from study tracking documentation and event-level impacts will be integrated to the EDC. Events that exceed 5% subject-level incidence of

the relevant analysis set will be used to exclude affected subjects from the analysis sets defined for sensitivity analyses. Events that do and do not exceed a 5% subject-level incidence of the relevant analysis set will be presented using descriptive statistics for the incidence of subject-level impacts via sensitivity analyses.

See also Section 4.3 for presentation of COVID-19 pandemic related subject disposition.

4.13 Changes from Planned Analyses in the Protocol

The following changes or additions to the planned analyses described in the study protocol are noted:

In Section 4.2 Determination of Sample Size, the assumption has been corrected from the protocol 'continuity-corrected Z-test with *unpooled* variances' to use 'continuity-corrected Z-test with *pooled* variances', as a technical correction.

The protocol defines an Intent-to-Treat (ITT) Set (all randomized subjects who have received at least one dose of study treatment) as the primary analysis population. The SAP further defines a modified Intent-to-Treat (mITT) Set (all randomized subjects who have been dispensed [redacted] dose of study treatment as the primary analysis population for the primary efficacy endpoint

The SAP also further defines the uniform Intent-to-Treat (uITT) Set as the supportive analysis population for the primary efficacy endpoint.

[redacted]

Prior versions of the SAP have included an analysis of IGA (scalp only) in the ITT Set among subjects enrolled under the original protocol. This is no longer considered determinative for evaluating the effect of therapy in the indication of moderate to severe scalp psoriasis and so the analysis is moved to the 'Other Secondary' section.

[redacted]

[redacted]

Sensitivity analyses are revised to include only primary and key secondary endpoints, since other secondary efficacy endpoints are less meaningful to the objectives of the study.

Section 4.11 defines examinations of subgroups and sensitivity analyses.

Multiple sections identify removal of sensitivity analyses related to secondary endpoints. Section 3 defines dose-relative criteria for completion of Part 1 and initiation of Parts 2 and 3 of the protocol.

Handling of COVID-19 pandemic-related events are specified in the SAP in the sections shown below:

- 4.3 Disposition of Subjects,
- 4.5 Protocol Deviations,
- 4.8 Study Drug Exposure and Compliance,

- 4.9.1 Primary Estimand and Intercurrent Events,
- 4.12 COVID-19 Pandemic Impacted Subject Assessments

Section 4.9.6 describes by-subject displays

Section 6.2.1 describes COVID-19 impacts to Visits

Section 6.2.4 describes SAS® Procedures for M-N methodology implementation

[redacted]

6 PROGRAMMING CONSIDERATIONS

All tables, data listings, figures (TLFs), and statistical analyses will be generated using SAS® Version 9.4 or above. Generated outputs will adhere to the following specifications.

6.1 Table, Listing, and Figure Format

6.1.1 General

1) All TLFs will be produced in landscape format.
2) All TLFs will be produced using the Courier New font, size 8.
3) The data displays for all TLFs will have a 1.5-inch binding margin on top of a landscape oriented page and a minimum 1-inch margin on the other 3 sides.
4) Headers and footers for figures will be in Courier New font, size 8.
5) Legends will be used for all figures with more than 1 variable, group, or item displayed.
6) TLFs will be in black and white (no color).
7) Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs. On some occasions, superscripts 1, 2, or 3 may be used (see below).
8) Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain superscripts (e.g., cm^2) will be employed on a case-by-case basis.
9) Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats.

6.1.2 Headers

1) All output should have the following header at the top of the page:

Sun Pharmaceutical Industries Ltd Status – Draft/Final Page n of N

Study: TILD-18-20 Interim/Final Analysis

All output should have page number. TLFs should be internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table, listing or figure).

6.1.3 Display Titles

Each TLF should be identified by a numeral, and the designation (i.e.,

1) Table 1) should be centered above the title. A decimal system (Table 14.x.y.z, Figure 14.x.y.z, and Listing 16.2.x.y) should be used to identify TLFs with related contents. The title is centered in initial capital characters. The analysis set should be identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the column headers. There will be 1 blank line between the last title and the solid line.

Table 14.x.y.z
First Line of Title
Second Line of Title if Needed
FAS

6.1.4 Column Headers

1) Column headings should be displayed immediately below the solid line described above in initial upper-case characters.
2) For numeric variables, include “unit” in column or row heading when appropriate.
3) Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings if applicable). This is distinct from the ‘n’ used for the descriptive statistics representing the number of subjects in the analysis set.
4) The order of treatments in the tables and listings will be: Placebo and Tildrakizumab 100 mg, and Total (if applicable).

6.1.5 Body of the Data Display

1) Listings data will be sorted for presentation in order of treatment groups as above, subject ID, collection day, and collection time.
2) If the categories of a parameter are ordered, then all categories between the maximum and minimum category should be presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	n
severe	0
moderate	8
mild	3

Where percentages are presented in these tables, any counts of 0 will be presented as 0 and not as 0 (0%).

3) If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups should be included.
4) An Unknown or Missing category for categorical summarization should be added to any parameter for which information is not available for 1 or more subjects.
5) Unless otherwise specified, the estimated mean and median for a set of values should be printed out to 1 more significant digit than the original values, and standard deviations should be printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

n	XX
Mean	XXX.X
SD	X.XX
Median	XXX.X
Range	(XXX, XXX)

6) All p-values should be output in the format: "0.xxxxx", where xxx is the value rounded to 5 decimal places. Any p-value less than 0.00001 will be presented as <0.00001.
7) Data in columns of a table should be formatted as follows:
   - alphanumeric values are left-justified;
   - whole numbers (e.g., counts) are right-justified; and
   - numbers containing fractional portions are decimal aligned.
8) Percentage values should be printed with 1 digit to the right of the decimal point in parentheses set 1 space after the count (e.g., 7 (12.8%), 13 (5.4%)). Less-than-signs

"<0.1%" should be printed when values are >0.0% and <0.1% (not 0.0%). Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment group who have an observation will be the denominator.

9) Tabular display of data for prior / concomitant medications, and all tabular displays of adverse event data should be presented by the body system, drug class, or SOC with the highest occurrence in the active treatment group in decreasing order. Within the body system, drug class and SOC, medical history (by PT), drugs (by ATC3 code), and adverse events (by PT) should be displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically.

10) Missing data should be represented on subject listings as either a hyphen ("-") with a corresponding footnote (" - = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate. For summary tables, missing descriptive statistics or p-values due to non-estimability should be reported as "-" with a corresponding footnote ("- = not estimable")..

11) Date should be printed in ISO date format ("yyyy-mm-dd": 2000-07-01). Missing portions of dates should be represented on subject listings as partial dates (2000-07). Dates that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.

12) All observed time values must be presented using a 24-hour clock HH:MM:SS format (e.g., 01:35:45, or 11:26). Time will only be reported if it was measured as part of the study.

6.1.6 Demographics and Baseline Characteristics

1) Age = (Date of informed consent - Date of birth + 1) / 365.25 and truncated to complete years.

2) Conversion factors and calculations for height, weight, and BMI:
   - Height (in cm) = height (in inches) * 2.54
   - Weight (in kg) = weight (in lbs) * 0.4536
   - BMI (kg/m^2) = Weight(kg)/[Height$(m)^2$]

3) The value of XX (e.g. age or day of assessment) will be calculated relative to a reference time point X (e.g. time of enrollment/first dose). If reference day/month is missing, the first day of the month/year will be used to create a SAS® date for variables 'Date of X '.

6.1.7 Footnotes

1) A solid line spanning the width between the left and right margins will separate the body of the data display from the footnotes.

2) All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.

3) Footnotes should always begin with "Note:" if an informational footnote, or asterisks and other non-numeric symbols if an annotated footnote. Each new footnote starts on a new line.
4) Footnotes will be present on the page where they are first referenced and thereafter on each page of the table, unless the footnote is specific only to certain pages. Subject specific footnotes should be avoided.
5) Footnotes will be used sparingly and must add value to the table, figure, or data listing. If more than 4 footnotes are planned, then a cover page may be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page. Footnotes should not repeat definitions already provided in the SAP.
6) The last line of the footnote section will be a standard source line that indicates the data source called in by the program, the name of the program used to produce the data display, and the listing source (i.e., 'Data source: xyzabc.sas7bdat Program source: myprogram.sas Listing source: 16.x.y.z').

6.2 Data-Handling Rules

This section describes naming conventions and rules for calculations that would be common to all applicable tables. Some rules specific to a table can be found in the relevant mock-ups.

6.2.1 Visits

1) Relative Study Day: The first day of treatment is Day 1. A minus (-) sign indicates days prior to the start of treatment (e.g., Day -5 represents 5 days before start of therapy. There is no Day 0. The relative study day for a specific post-baseline visit is calculated as (Visit Date - Date of First Dose +1).
2) Baseline: Evaluation taken on baseline visit or the last available evaluation prior to the first dose of study drug if the former is missing.
3) COVID-19 affected week 16 visit: by-subject listing will show imputed and modeled results. See Section 4.11 for additional details.

6.2.2 Prior and Concomitant Medications

1) Prior and concomitant medications will be coded and classified using the treatment start and stop dates relative to date of first study medication. The specific dictionary version will be provided in the actual tables/listings.
2) Counting rules for prior/concomitant medications: Prior medications refer to all medications that were taken within 6 months prior to enrollment and stopped prior to start of treatment. Concomitant medications refer to all medications that started at any time and were taken at any time after the start of treatment until the end of the entire treatment period including those continued from pre-treatment.
3) Medications missing both start and stop dates, or having a start date prior to the last dose of study drug and missing the stop date, or having a stop date after the start of

study drug and missing the start date, will be counted as concomitant. When partial dates are present in the data, both a partial start date and/or a partial stop date will be evaluated to determine whether it can be conclusively established that the medication either ended prior to the start of study drug or started after the end of study drug. If the above cannot be conclusively established based on the partial and/or present dates, then the medication will be counted as concomitant.

6.2.3 Safety

1) If multiple results (e.g., lab test results) are reported at a study visit, then the last available result reported for that visit will be used in that visit summary.
2) Adverse events will be coded and classified using MedDRA. The specific dictionary version will be provided in the actual tables/listings.
3) Counting rules for AEs: AEs with missing start dates, but with stop dates either overlapping into the treatment period or missing, will be counted as treatment-emergent, taking the worst-case approach. Special care will be taken regarding partial dates with similar logic to that of the prior/concomitant medications applied.
4) For purposes of flagging individual subject data, laboratory test result abnormalities are defined as values above or below the normal range.
5) Conversion factor for temperature:

   Temperature (in °C) = 5/9 (Temperature [in °F]-32).

   Conversion factors for ECG QT to QTcF if any subjects do not have reported QTcF values but have reported QT and RR values:

   Fridericia formula: $QTcF = QT / (RR^{1/3})$

6.2.4 SAS® Procedures

This section provides sample SAS® code to illustrate statistical tests specified in the statistical methods section. All computer output from SAS® statistical procedures serving as a basis for extracted results (e.g., MIXED, FREQ/CMH) will be retained for quality control procedures and will be included in CSR appendices.

1) The percentage change from baseline is calculated as the post-baseline score minus the baseline score, and the difference divided by the baseline score, expressed in units of percent. The mean percentage change is derived as the least squares mean for treatment/visit interaction from the mixed model shown in 4) below.
2) M-N Method:

   The M-N method will be used for the primary efficacy analysis, which provides point estimates for the difference between treatments, and their corresponding [redacted]

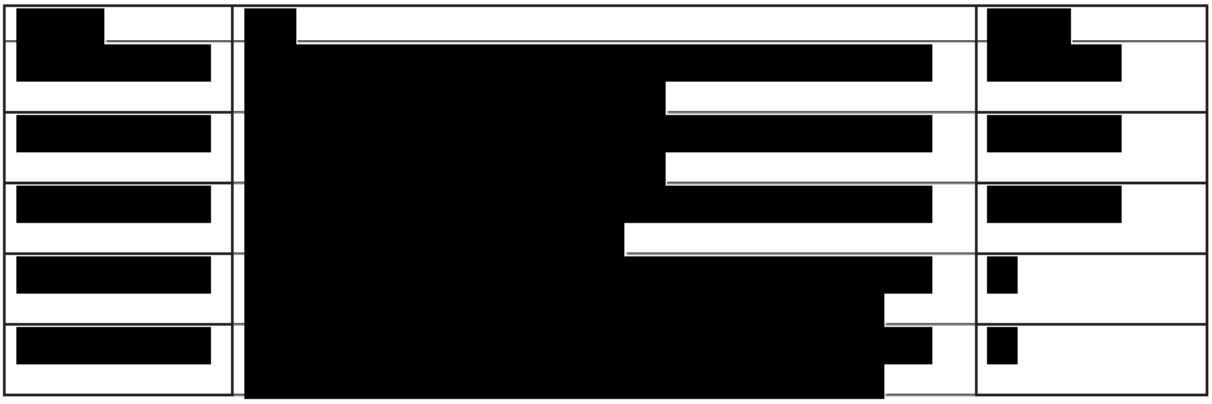
[redacted]

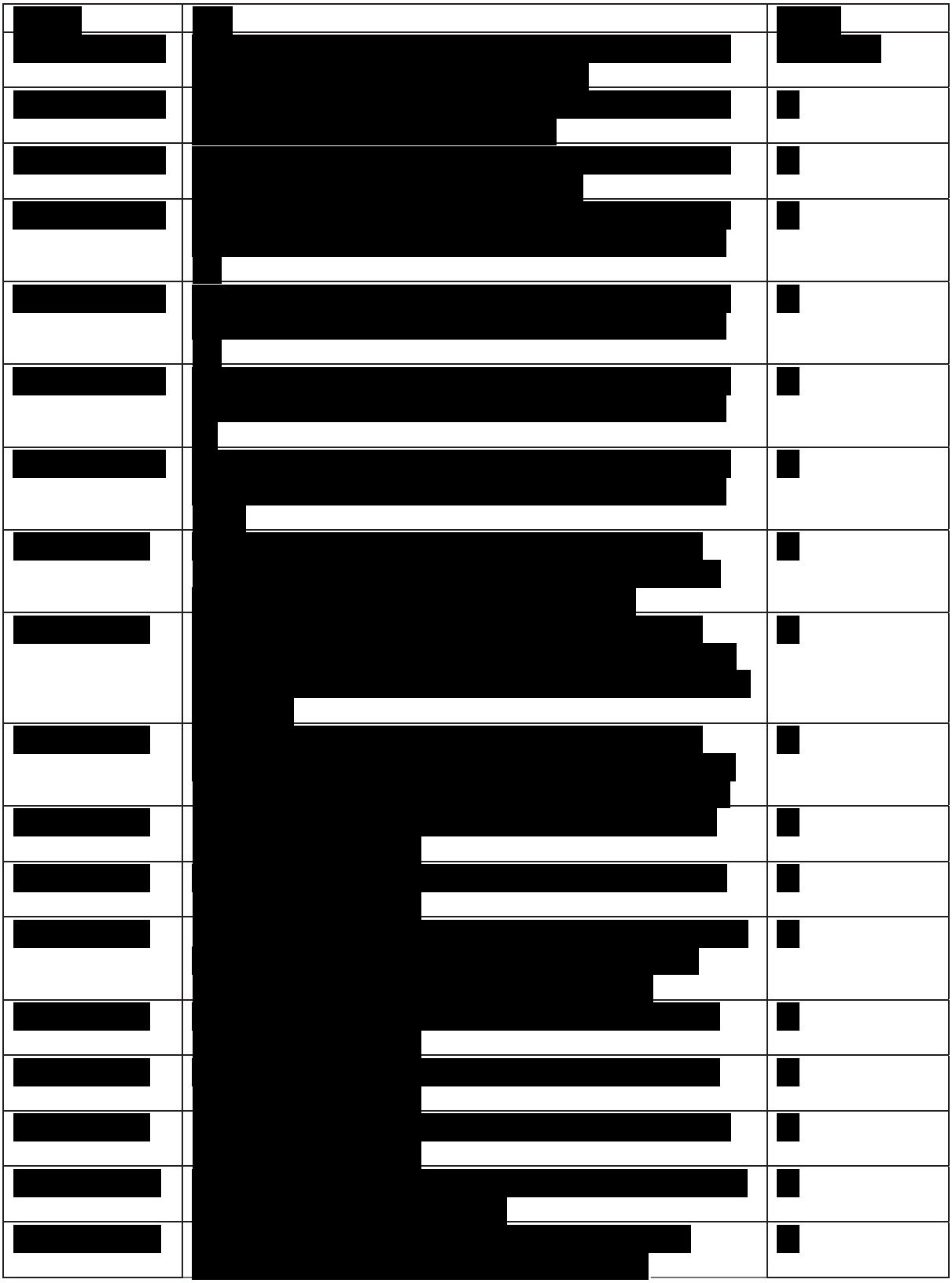
An unstructured (UN) covariance matrix will be used to fit each MMRM model. If the model does not converge using an unstructured covariance matrix, other covariance structures will be tested.

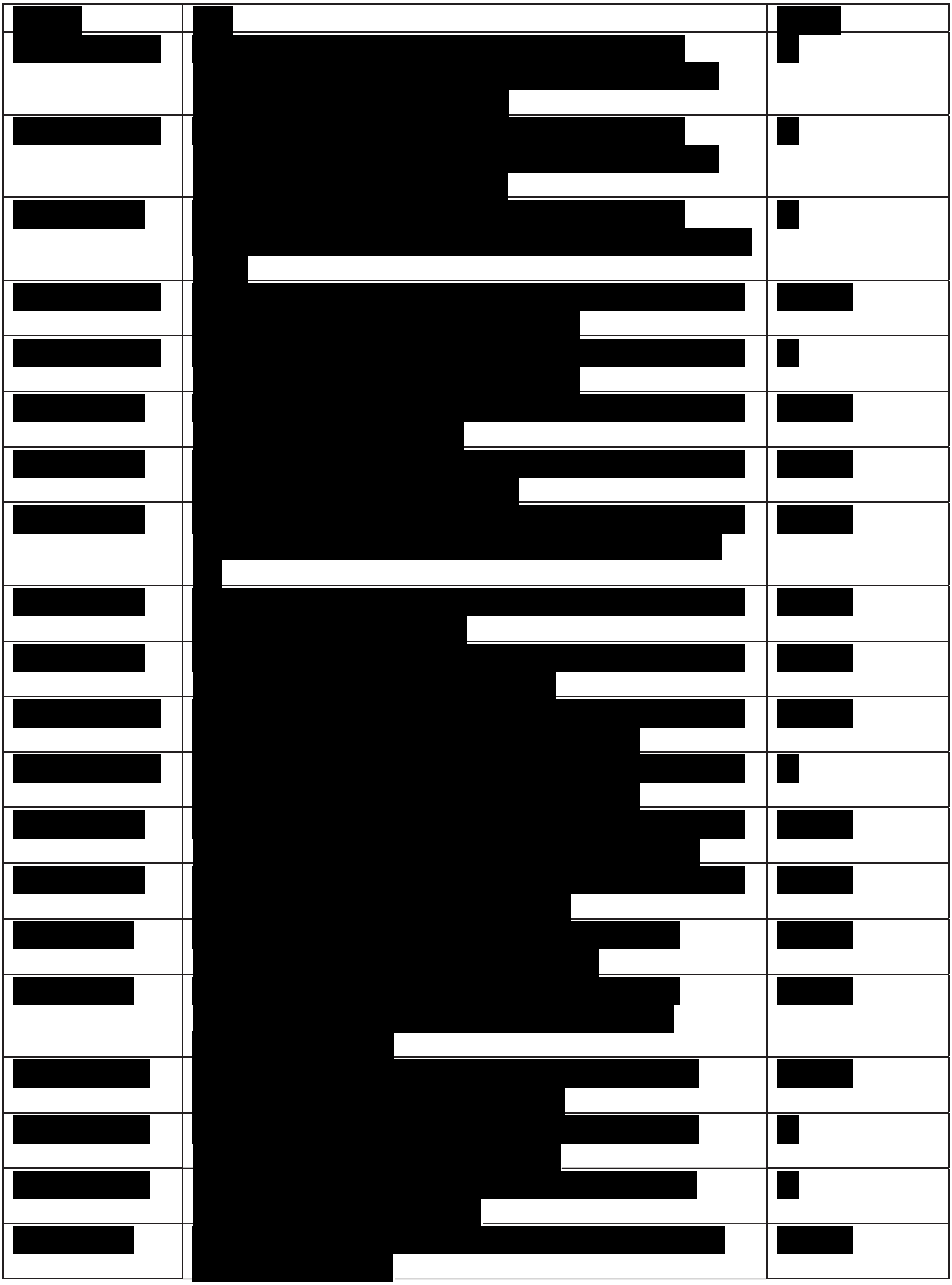
[redacted]

[redacted]

[redacted]







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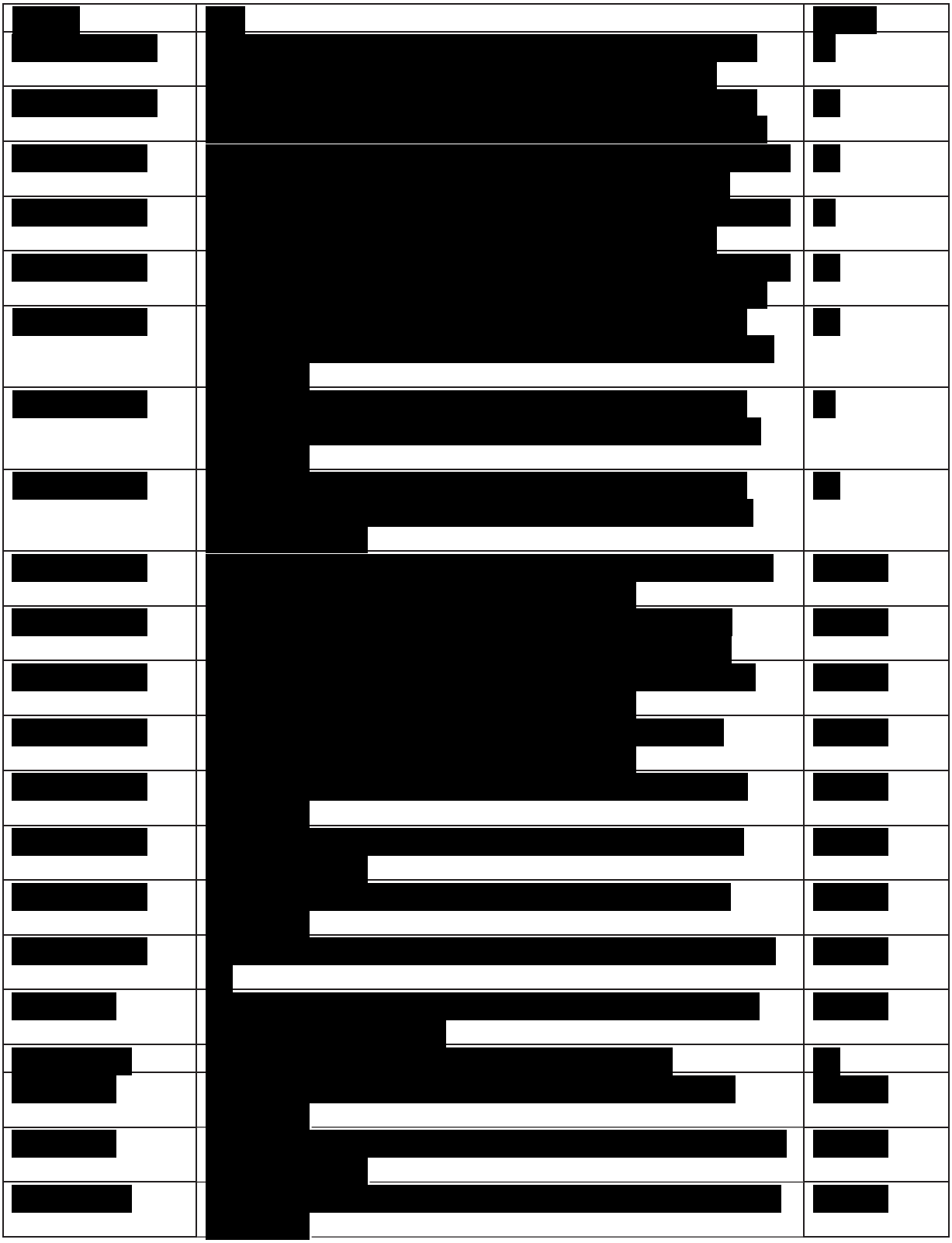

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[redacted]

APPENDIX 1 PASI SCORING

PASI is evaluated within each of the four body regions: a) head, b) upper limbs, c) trunk, and d) lower limbs;

[redacted]

APPENDIX 2 DLQI SCORING

The Dermatology Life Quality Index (DLQI) questionnaire is an assessment of treatment response on the subject's quality of life to measure how much the scalp psoriasis has affected the subject's life during the previous week. [redacted]

Electronic Record and Signature Disclosure created on: 4/9/2019 8:11:10 AM
Parties agreed to: Jin Wei, Larry Xie, Qingyuan Wu, Tushar Nishandar

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